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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/369,941	08/06/99	KENSIL C	106941.181

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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	15

DATE MAILED: 01/18/01

Please find below and/or attached an Office communication concerning this application r pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/369,941	KENSIL, CHARLOTTE A.	
	Examiner	Art Unit	
	Michael Wilson	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-32 and 49-62* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 33-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-32 and 49-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10 & 11* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group II, claims 19-32 and 49-62, in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-18 and 33-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Claims 19-32 and 49-62 are under consideration in the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 19-21, 24, 27, 29-32, 49-51, 54, 57 and 59-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Urban (Urban et al. US Patent 6,013,258, Jan 11, 2000).

Urban teaches combining a plasmid encoding an antigen with saponin/Quil A (col. 3, line 30; col. 6, lines 18-37). The $pBIOTOPE_{HPV}$ plasmid taught by Urban inherently has at least one unmethylated CpG dinucleotide as claimed because plasmids are bacterial DNA which inherently have unmethylated CpG dinucleotides. While not relied upon, the inherency of plasmid DNA having unmethylated CpG dinucleotides is supported by Krieg (Krieg et al., Tends in Microbiology, Jan. 1, 1998, Vol. 6, pages 23-26) who states that plasmid DNA is bacterial DNA that has unmethylated CpG dinucleotides (page 23, line 5; page 25, col. 1, p. 1 and 2). Saponin/Quil A is inherently derived from *Quillaja saponaria* and considered "substantially" pure because the term "substantially" is not defined in the specification and because saponin must be purified away from other compounds to be obtained which is considered "substantially pure".

The $pBIOTOPE_{HPV}$ plasmid having unmethylated CpG dinucleotides as taught by Urban is equivalent to the unmethylated CpG dinucleotide claimed because the specification states the CpG dinucleotide may be a part of a vector (page 8, line 16), because the $pBIOTOPE_{HPV}$ plasmid is a vector and because the claims use open language encompassing sequences having the oligonucleotide sequence within a plasmid.

Claims 27 and 57 are anticipated by Urban because the $pBIOTOPE_{HPV}$ plasmid inherently has at least one motif of $5'X_1CGX_2 3'$ as claimed. The phrase "wherein at least one nucleotide separates consecutive CpGs" is anticipated by Urban because only one CpG sequence is required and because of the indefiniteness of the claims (see 112/2nd below).

Claims 32 and 62 are anticipated by Urban because the composition comprises a nucleic acid encoding an antigen and because of the indefiniteness of the claim (see 112/2nd below).

The phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" is an intended use in claims 29-31 and does not bear patentable weight in determining the structure or function of the composition being claimed because it does not necessarily occur and because it does not clearly describe the structure or alter the function of the composition.

However, in claims 59-61 which are method claims, the phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" does bear patentable weight because the claims recite a positive limitation that the effect occurs. Claims 59-61 are anticipated by Urban because Urban teaches administering the nucleic acids of the invention in combination with saponin (col. 6, line 18) and administering the composition to humans (col. 2, line 24) and because co-administration of the plasmid and saponin/Quil A would inherently increase the immune response to the antigen as claimed. Saponin and unmethylated CpG dinucleotides inherently increase the immune response. While not relied upon, Krieg again supports the inherent ability of plasmid DNA to enhance the immune response by stating unmethylated CpG dinucleotides are found in plasmid DNA and enhance the immune response to antigen encoded by the plasmid (page 24, last paragraph).

Thus, Urban anticipates the claims.

3. Claims 19-24, 27, 29-32 and 49-54, 57, 59-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Sasaki (Sasaki et al. US Patent 5,808,024, Sept. 15, 1998).

Sasaki teaches the pBluescript II SK plasmid encoding an antigen (col. 18, lines 4-19; col. 11, lines 22-45) and combining such nucleic acids with QS21 (column 3, lines 36-63; see especially lines 39 and 63). Plasmid DNA such as the pBluescript II SK vector taught by Sasaki inherently has at least one unmethylated CpG dinucleotide as claimed because plasmids are bacterial DNA which inherently has unmethylated CpG dinucleotides. While not relied upon, the inherency of plasmid DNA having unmethylated CpG dinucleotides is supported by Krieg (Krieg et al., Tends in Microbiology, Jan. 1, 1998, Vol. 6, pages 23-26) who states that plasmid DNA is bacterial DNA that has unmethylated CpG dinucleotides (page 23, line 5; page 25, col. 1, p. 1 and 2). QS21 is inherently derived from *Quillaja saponaria* and is considered "substantially" pure because the term "substantially" is not defined in the specification and because QS21 must be purified away from other compounds to be obtained which is considered "substantially pure".

A plasmid having unmethylated CpG dinucleotides as taught by Sasaki is equivalent to the unmethylated CpG dinucleotide claimed because the specification states the CpG dinucleotide may be a part of a vector (page 8, line 16), because a plasmid is a vector and because the claims use open language encompassing sequences having the oligonucleotide sequence within a plasmid.

The limitation of the CpG motif having the formula $5'X_1CGX_2 3'$ as claimed is equivalent to the nucleotide sequence of Fig. 6B, nucleotides 696-700 (TCGC), 794-797 (ACGC) and elsewhere, which have the equivalent formula. The phrase "wherein at least one nucleotide

separates consecutive CpGs" is anticipated by the sequence of Fig. 6B because nucleotides 696-700 and 794-797 are separated by 93 nucleotides.

Claims 32 and 62 are anticipated by Sasaki because the composition comprises a nucleic acid encoding an antigen and because of the indefiniteness of the claim (see 112/2nd below).

The phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" is an intended use in claims 29-31 and does not bear patentable weight in determining the structure or function of the composition being claimed because it does not necessarily occur and because it does not clearly describe the structure or alter the function of the composition.

However, in claims 59-61 which are method claims, the phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" does bear patentable weight because the claims recite a positive limitation that the effect occurs. Claims 59-61 are anticipated by Sasaki because Sasaki teaches administering the nucleic acids of the invention in combination with QS21 to humans (paragraph bridging col. 3 and 4; see col. 3, line 45) and because co-administration of the plasmid and QS21 would inherently increase the immune response to the antigen as claimed. Sasaki teaches QS21 is an adjuvant; adjuvants inherently increase the immune response. Plasmid DNA inherently has unmethylated CpG dinucleotides which inherently increase the immune response. While not relied upon, Krieg again supports the inherent ability of plasmid DNA to enhance the immune response by stating

unmethylated CpG dinucleotides are found in plasmid DNA and enhance the immune response to antigen encoded by the plasmid (page 24, last paragraph).

Thus, Sasaki anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 19-32 and 49-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Weiner et al., Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55).

Weiner teaches co-administration of the oligonucleotide 1758 and tumor antigen to mice increases the immune response against the antigen (see page 10834, col. 1, "CpG ODN 1758 was most effective as an adjuvant at enhancing production of anti-Id following immunization with Id-KLH). Oligonucleotide 1758 ~~is~~ has unmethylated CpG dinucleotides and is equivalent to SEQ ID NO:1 as claimed (page 20, line 9 of the instant application). Weiner does not teach combining the unmethylated CpG dinucleotides with saponin.

However, at the time of filing, Kensil taught combining purified QS21 isolated from *Quillaja* with tumor antigens and administering the composition to individuals with cancer to

increase the immune response of the individual to tumor (see page 26 and page 23). The purified QS21 of Kensil is "substantially pure" as claimed because it is purified.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the oligonucleotide 1758/tumor antigen composition of Weiner with QS21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increase the immune response to an antigen administered to an individual with cancer and 2) both the oligonucleotide and the QS21 adjuvants could be combined with the antigen because it was common for one of ordinary skill in the art at the time of filing to use more than one adjuvant to increase the immune response to antigen. In addition, Weiner discusses QS21 used as an adjuvant to deliver tumor antigen and suggests combining the oligonucleotide/antigen composition with other adjuvants to determine synergistic adjuvant effects (pages 10835, 4 lines from the end; page 10836, col. 2, second to last sentence). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to add QS21 to the oligonucleotide 1758/tumor antigen composition to increase the immune response to the tumor antigen.

Claims 32 and 62 are obvious in view of the combined teachings of Weiner and Kensil because the composition comprises an antigen and because of the indefiniteness of the claim (see 112/2nd below).

The phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" is an intended use in claims 29-31 and does not bear patentable weight in determining the structure or function of the composition being claimed because it does not necessarily occur and because it does not clearly describe the structure or alter the function of the composition.

However, in claims 59-61 which are method claims, the phrase "wherein the composition increases the immune response to an antigen when administered to a mammal," "human" or "animal" does bear patentable weight because the claims recite a positive limitation that the effect occurs. Claims 59 and 61 are obvious in view of the combined teachings of Weiner and Kensil because the Weiner and Kensil teaches administering the antigen in combination with unmethylated CpG dinucleotides and QS21, because Weiner teaches administering unmethylated CpG dinucleotides and antigen to mice and increasing the immune response (page 10835, parag. bridging col. 1 and 2), because co-administration of the antigen/oligonucleotide/QS21 would inherently increase the immune response to the antigen as claimed. Reliance upon inherency is not improper even though this rejection is based on Section 103 instead of Section 102 (In re Skoner, et al. 186 USPQ 80 (CCPA)).

Weiner does not teach administering the composition to humans or increasing the immune response in humans. It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the composition to humans because Weiner teaches administering the adjuvant/antigen to mice which is a well-established model for humans (page

10833, col. 2, line 18). One of ordinary skill in the art at the time the invention was made would have been motivated to administer the composition to humans to protect from tumor growth (Weiner, page 10835, col. 1, line 7).

Thus, the combined teachings of Weiner and Kensil teach all the limitations of the claimed invention. Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 32 recites the limitation "antigen" in claim 27 which depends on claim 24 which depends on claim 19. There is insufficient antecedent basis for this limitation in the parent claims.

Claims 29-31 and 59-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if applicants are attempting to further limit the claim to administering a composition comprising the dinucleotide/saponin and an antigen or to administering a composition comprising the dinucleotide/saponin and increasing the immune response to an antigen that is administered to the mammal at a later time. Clarification is required.

In claims 32 and 62, "antigens" comprise amino acid/polypeptide sequences and do not comprise proteins, peptides, polysaccharides, lipids, glycolipids, phospholipids or nucleic acid sequences. The terms used do not further limit the antigen. Clarification is required.

Claims 27 and 57 are indefinite because the phrase "wherein at least one nucleotide separates consecutive CpGs" is unclear. The parent claims only require at least one unmethylated CpG dinucleotide. Therefore, it is unclear if applicants intend to further limit the oligonucleotide to comprise at least two CpGs or if the oligonucleotide merely comprise at least one CpG.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 305-0196.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

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Michael C. Wilson

AU1633

MICHAEL C. WILSON
PATENT EXAMINER